traverses. While these papers may discuss the identification of critical sites, neither Park et al., Endo et al., or Badger et al. mention the importance of the location of a critical site **within the minor groove** of an RNA molecule, as claimed.

Park et al. disclose that the $G^3.U^{70}$ base pair in the acceptor helix of $tRNA^{Ala}$ is necessary for aminoacylation by alanyl-tRNA synthetase and show that substitution of the $G^3.U^{70}$ base pair with an $A^3.U^{70}$ base pair inhibits aminoacylation. Park et al. do not determine the relationship of the critical site to the three-dimensional structure of the tRNA molecule and therefore fail to appreciate whether it is the major groove, minor groove, polynucleotide backbone or some other feature that is critical for the alanyl-tRNA synthetase. That the critical part of the $G^3.U^{70}$ site **is within the minor groove** and can therefore be accessed and blocked by the binding of a molecule having a complementary structure is not taught. Park et al. certainly fail to teach, suggest or imply that compounds, such as complementary molecules that can bind to and block a critical site in the minor groove, are useful for the inhibition of RNA function such as protein synthesis as claimed in the present application.

In the Office Action, the Examiner states that Park et al. have determined the three dimensional location of a critical site, namely "in the acceptor helix". The Examiner then refers

applicant to page 2714 of the paper. Applicant respectfully submits that the paper by Park et al. begins on page 2740 of the 28th volume of the journal *Biochemistry* and does not contain a page numbered "2714". Applicant assumes that this is a typographical mistake and that the Examiner intended for applicant to be directed to page 27**41**, which discusses Figure 1a, located on page 2742, which shows the sequences and cloverleaf structures of $tRNA^{Ala/UGC}$ and $tRNA^{Ala/CUA}$. Figure 1a is a **two-dimensional drawing** and cannot possibly show the three-dimensional conformation of the minor and major grooves and other features of the molecule as shown in Figure 1A of the present application. Furthermore, applicant can find no mention of tertiary structure of the tRNA molecule and definitely can find no description of the location of a minor groove and its relationship to the critical site.

Endo et al. disclose the importance of the primary and secondary structural features necessary for the protein α-sarcin to recognize and cleave rRNA, but fail to determine the tertiary structure of the rRNA and its importance in RNA function. In the Office Action, the Examiner states that Endo et al. determined the three-dimensional structure surrounding the targeted site, referencing page 2216. Applicant cannot find where on page 2216 the authors describe this three-dimensional structure. Applicant notes that, on this page, the authors mention that their

synthetic oligoribonucleotide presumably reproduces certain known structures of rRNA at the site of modification. These structures described by Endo et al. are "a stem, a bulged nucleotide, and a loop" (p. 2216 and p. 2217). Applicant respectfully submits that such structures are two-dimensional, as shown in Figure 1A of Endo et al., not three-dimensional. Nowhere in the Endo et al. paper do the authors describe the three dimensional structure of the rRNA molecule and the importance of identifying the critical site within a three dimensional structure such as the minor groove.

Badger et al. disclose the three-dimensional, x-ray crystallographic analysis of the binding of antiviral WIN compounds to the **viral protein coat** of native and drug-resistant human rhinovirus. (See Figure 1 of Badger et al., on page 164, showing the binding of a compound within the "pore" or "Win pocket" of the protein coat of a human rhinovirus) Badger et al. suggest that antiviral drugs could be developed that have the correct orientation to bind to these mutated proteins. Badger et al. sequence the RNA encoding the deformed WIN pocket of the mutants and discover single base changes encoding amino acids that interfere with the binding, however, Badger et al. never extend their analysis to determine the secondary or tertiary structure **of the RNA** because the WIN compounds bind to the protein itself, not the RNA encoding the protein. Badger et al.

are entirely concerned with the structure of mutant proteins, not RNA, and certainly do not suggest the design of drugs that would inhibit RNA function by binding in the minor groove of an RNA molecule.

The identification of the general location of a critical site that is essential for function is a useless piece of information for therapeutic purposes unless the subset of atoms within that site that are needed for function can be defined **along with their spatial arrangement.** In other words, if one cannot access and impair the function of the critical site, then no successful therapy can be developed.

Applicant respectfully submits that the Examiner is thinking of the two-dimensional cloverleaf structure of the tRNA molecule and not of the three-dimensional structure with major and minor grooves and other features. The mere fact that a critical site is located in the amino acid acceptor helix of a tRNA molecule does not provide any information regarding the spatial arrangement of the atoms that make up that part of the critical site that is needed for function. The cloverleaf structure is folded into a highly differentiated structure in three dimensions. The importance of the critical atoms being in or part of the minor groove of an RNA helix is that they are then within a wide, shallow area of the RNA molecule that is accessible to an inhibitory binding compound that is

complementary in three dimensions to just the subset of atoms needed for function.

Applicant does not understand the Examiner's comment on page 4 of the Office Action mailed January 26, 1994 in parent application U.S.S.N. 08/129,787, stating that applicant has not shown that the critical site would always be in a minor groove. The major and minor grooves of a nucleic acid molecule are not formed in an arbitrary manner, they are determined from the primary nucleotide sequence, which is constant. In order to practice the claimed invention, one skilled in the art must sequence the critical site, determine the secondary and three-dimensional structure of the region in which the critical site is located, determine whether any part of the critical site is located within a minor groove, and, if it is, synthesize a compound that will bind to those atoms that make up the critical site within the minor groove. If no part of the critical site is within a minor groove, then the inhibition of RNA function by the claimed method cannot occur.

Applicant respectfully submits that, in view of the foregoing remarks, the claimed methods and compounds are not obvious in view of the references cited by the Examiner, taken alone or in combination, which fail to describe the importance of locating the atoms that make the site critical and delineating those, if any, in the minor groove.

Rejection Under 35 U.S.C. §112, first paragraph

In the Office Action mailed January 26, 1994, the Examiner maintained the objection to the specification and rejected claims 1 and 3-19 under 35 U.S.C. §112, first paragraph, on the basis that the claims were not enabled by the specification. In particular, the Examiner implied that processes essential to the determination of the critical site of function, the location of minor groove, and how to design drugs were incorporated by reference and that applicant was required to amend the specification to include the material incorporated by reference. Applicant has amended the specification to include the material incorporated by reference as required by the Examiner and has deleted the incorporation by reference clause from page 39.

Applicant respectfully submits that the foregoing amendments and remarks overcome the rejections of the Examiner. In addition, applicant notes that the dependent claims provide additional guidance on how one skilled in the art should make and use the claimed methods and compounds. For example, Claim 6 describes how the three-dimensional structure of the RNA molecule is determined, Claims 7 and 8 describe how the critical region is determined, Claims 14 and 17 describe the critical site as within the minor groove of the acceptor stem of a tRNA molecule, Claims 15 and 18 define the tRNA molecule as $tRNA^{Ala}$, and Claims 16 and

19 specifically define the critical region as the G3:U70 base pair.

Applicant submits that Claims 1, and 3-19 are in condition for allowance. A Notice of Allowance is therefore respectfully solicited.

Respectfully submitted,

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Date: May 26, 1994

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CERTIFICATE OF MAILING UNDER 37 CFR § 1.10

I hereby certify that this paper and any documents referred to as attached therein are being deposited with the United States Postal Service on the date indicated below with sufficient postage in an envelope as "Express Mail Post Office to Addressee" service under 37 C.F.R. §1.10, Mailing Label Number TB278055217US addressed to Box FWC, Commissioner of Patents and Trademarks, Washington, D.C. 20231.

May 26, 1994

Terri M. Holbrook